

Cross-reactivity of alternate plant sources of latex in subjects with systemic IgE-mediated sensitivity to *Hevea brasiliensis* latex

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Andrew B. Carey, MD*; Katrina Cornish, PhD†; Paula Schrank‡; Bonnie Ward‡; and Ronald Simon, MD‡

Background: Previous studies have suggested that there is cross-reactivity in subjects sensitive to natural rubber proteins with other plant proteins such as banana, chestnut, and avocado. There are numerous other plants known to produce rubber including *Parthenium argentatum* and *Ficus elastica*. It is not known whether patients with IgE-mediated systemic reactions caused by the common source of natural rubber *Hevea brasiliensis* are also sensitive to the rubber-containing material from these other plant sources of latex. It is also not certain how much the allergenicity of latex made from *Hevea brasiliensis* can be reduced by extracting proteins from the sap since some proteins are tightly associated with the cis-1,4-polyisoprene.

Objective: In this study we investigated whether there would be cross-reactivity to other natural sources of latex in these patients.

Methods: Seven patients with histories of systemic type I hypersensitivity to latex products had strongly positive skin tests to *Hevea brasiliensis* latex from two different sources. These subjects were tested by the prick method for sensitivity to three other natural sources of latex. These included latex-containing material from *Parthenium argentatum* and *Ficus elastica* as well as washed and centrifuged rubber particles from *Hevea brasiliensis* sap.

Results: All subjects had negative skin tests to all dilutions of the rubber samples from other natural sources of latex.

Conclusion: These results suggest several potential sources of natural hypoallergenic latex that might be tolerated by latex-sensitive individuals.

INTRODUCTION

There have been numerous reports of anaphylaxis and urticaria due to rubber products made from the sap (latex) of the tropical rubber tree *Hevea brasiliensis* since the initial case of immediate hypersensitivity to a latex product was reported in 1979.

An increased incidence of this problem in health care workers and patients with spina bifida has been well described. Recent studies such as that of Iacobelli disclosed positive latex skin

test reactions in 14.4% of operating room personnel.² Skin testing with latex extract was positive in 9.9% of 101 hospital physicians who regularly used latex gloves.³ Skin tests to latex were positive in 10.7% of 197 operating room nurses with positive skin tests observed to be 4.4 times more common in atopic individuals.⁴

A study of 32 patients with spina bifida disclosed IgE antibodies to latex antigens in 34%.⁵

The general public may also be at greater risk than previously thought. Skin tests on 80 consecutive children from the general population seen in an allergy clinic were positive in 3.8%.⁶

Cis-1,4-polyisoprene is a hydrocarbon made by more than 2,000 species of plants from about 300 genera and at least two fungal genera.^{7,8} Latex products are made by vulcanization which

cross links this polymer. The higher the molecular weight of the polyisoprene the better suited it is for high performance commercial uses. It is not known whether other natural sources of latex contain proteins that would cross react immunologically with *Hevea brasiliensis*.

Over 99% of the latex products made from natural sources come from *H. brasiliensis*, which makes a high molecular weight polyisoprene (approximately 1,500,000 daltons). The plant makes latex in laticifers, which are pipe-like structures under the bark.

Parthenium argentatum is a desert bush that grows in the southwestern United States and Mexico. It produces significant quantities of high molecular weight polyisoprene in parenchyma cells of the stem bark. It is also well known that the polyisoprene from this plant is well suited for production of numerous rubber products.⁹⁻¹¹

Ficus elastica is the common ornamental rubber plant. Like *H. brasiliensis* it produces natural rubber in laticifers, but of relatively low molecular weight.

The polyisoprene in all three of these plants occurs in subcellular rubber particles that also contain proteins some of which are necessary for rubber production.

There are currently available synthetic rubber gloves and other items made from oil that do not cause reactions in individuals with type I allergy to natural *H. brasiliensis* latex. These items have some limitation on their usefulness due to greater expense and in some cases due to a loss of "feel."

The purpose of this study was to use skin testing to determine whether patients with immediate hypersensitivity

* Woodland Clinic, Woodland, California.
† U.S. Department of Agriculture, Albany, California.
‡ Scripps Clinic and Research Institute, La Jolla, California.

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to *H. brasiliensis* latex proteins are also sensitive to selected alternative sources of natural polyisoprene. These include *P. argentatum*, *F. elastica*, and washed rubber particles from *H. brasiliensis*.

MATERIALS AND METHODS

Latex Products

Hevea brasiliensis sap or latex was obtained from two different sources. Ammoniated *H. brasiliensis* latex, which is more commonly available to the practicing allergist, was kindly supplied by Killian Latex, Akron, Ohio. Nonammoniated *H. brasiliensis* latex was obtained from Sumatran plantation trees (line PB 260); collected and mixed with two volumes of stabilization buffer [0.07 M NaHCO₃, 33% glycerol, 0.2% NaN₃, 3mM cysteine].

F. elastica latex was tapped from stems and petioles by removing the apical portion of the plants. It was suspended in an equal volume of buffer [100 mM Tris-HCl at pH 7.5, 1.2 mM MgSO₄ and 35% glycerol].

Washed rubber particles of *H. brasiliensis* and *F. elastica* were prepared by repeated centrifugation and resuspension in cold wash buffer.¹²

Rubber particles of *P. argentatum* are to some extent "washed." This is because they occur in bark parenchyma cells which must be homogenized to extract them using the following procedure. *P. argentatum* latex was prepared by homogenizing 70 g of peeled stem bark from stems of greater than 0.5 cm diameter in buffer [100 mM Tris-HCl, pH 7.5, 50 mM KF, 1% ascorbic acid, 5 mM MgSO₄, 6 mM 2-mercaptoethanol, 0.1 mM phenylmethylsulphonyl fluoride, 17.5 µL anti-foam A and 30 g polyvinylpyrrolidone]. The homogenate was filtered through eight layers of cheesecloth and centrifuged three times at 2400 g to 4000 g for seven to eight minutes [0.07 M NaHCO₃, 33% glycerol, 0.2% NaN₃, 3mM Cysteine] by a procedure previously described.¹³

The percent of solids in each sample was determined by dry down and found to range from 20.7% to 35.6%

with 95% of this weight attributable to isoprene. Total protein concentrations determined by Lowry assay were between 1 mg/100 mL and 3.3mg/100 mL.

Subjects

Subjects were obtained by solicitation and completing a questionnaire. Seven female patients 27 to 48 years of age, four of whom were atopic, with histories of immediate hypersensitivity reactions to latex products were interviewed and participated in skin testing. Primary exposure to latex in all cases was occupational as nurse, laboratory technician, or physician. All reported 4 month to 8 year histories of hives at the point of contact and immediate involvement of at least one distant site such as itchy eyes, runny nose, or wheezing.

All subjects were asked for and gave informed consent. Protocols were approved by the institutional review boards of Scripps Clinic and Research Foundation and the Woodland Clinic Medical Foundation.

Cutaneous tests by the prick method using the Morrow Brown lancet were performed sequentially beginning with a 1:10,000 dilution of concentrate material and increased by 10-fold dilutions until a positive skin test or negative skin test with concentrate was reached. A positive test was defined as a wheal measured as an average of two perpendicular diameters greater than that of the histamine control at 20 minutes.

Controls were histamine 1 mg/mL and 0.9% saline. Three control subjects with no history of latex allergy were also tested.

RESULTS

All patients tolerated the procedure well reporting only local itching at the positive skin test sites.

The results of skin testing are summarized in Table 1. Both the ammoniated and the nonammoniated preparations of unwashed *H. brasiliensis* latex elicited a positive skin test in all subjects. In each subject both preparations caused a consistently positive response

with the ammoniated preparation generally causing slightly smaller reactions.

The solutions of *F. elastica* latex and *F. elastica* washed rubber particles and *P. argentatum* washed rubber particles did not cause any positive skin response beyond saline control.

No patient had a wheal on skin response to the washed preparation of *H. brasiliensis*. All seven subjects, however, had a small amount of flare greater than that of saline control and the other washed rubber particles but less than half that of histamine.

DISCUSSION

IgE-mediated immediate hypersensitivity reactions to natural rubber latex products are almost always shown to be due to specific antibodies directed at constituent proteins from *H. brasiliensis* in the rubber products. Exceptions include one patient sensitive to terpenes and two patients reportedly sensitive to cornstarch.^{14,15} The specific protein or proteins are not known and there may be several. Investigations using various techniques have identified different causative antigens. These range in molecular weight from 2,000 to 100,000 daltons.¹⁶⁻²¹

The possibility of cross-reactivity between latex antigens and other plant proteins has been suggested. Several reports have documented latex-sensitive patients who were also sensitive to various fruits with RAST inhibition suggesting cross-reactivity in each case. M'Raihi described one patient sensitive to banana; Lavaud, one patient sensitive to both banana and avocado.^{22,23} Rodriguez reported three patients sensitive to banana, two of whom were also sensitive to chestnut.²⁴ Fernandez reported one patient cross-reactive to chestnut and one other patient cross-reactive to banana.²⁵ There may be other cross-reactive proteins that have not yet been described.

The current treatment for latex hypersensitivity consists of avoidance of all latex products, which can be quite difficult in today's hospitals. In addition it is recommended that sensitive

Table 1. Concentrations at which Seven Subjects Demonstrated Positive Skin Response to Different Preparations of Latex

Test Material	Concentrate	Dilution			
		1/10	1/100	1/1000	1/10,000
Ammoniated <i>H. brasiliensis</i> latex	3	1	3	0	0
<i>H. brasiliensis</i> latex	1	2	3	1	0
<i>H. brasiliensis</i> WRP*	0†	0	0	0	0
<i>F. elastica</i> latex	0	0	0	0	0
<i>F. elastica</i> WRP	0	0	0	0	0
<i>P. argentatum</i> WRP	0	0	0	0	0

* WRP (washed rubber particles).

† 0 denotes negative skin test in all patients.

patients undergoing surgery be prophylactically treated similar to patients with a history of radiocontrast media reactions; however, the effectiveness of such prophylactic treatment for latex allergy has not been well established. Even when the diagnosis is made and these precautions are taken some patients still have inadvertent exposures to rubber with severe reactions.²⁶

Data reported previously by Siler and Cornish suggest that there is rationale for rendering *H. brasiliensis* latex less allergenic by washing the rubber particles or that the allergen may be avoided by using an alternate source. SDS-PAGE electrophoresis has shown that most of the proteins in *H. brasiliensis* latex are not associated with the polyisoprene-containing rubber particles; therefore, by isolating the rubber one avoids most of the proteins that could be potential allergens (personal communication, Dr. Katrina Cornish).

This raises the question that perhaps the *P. argentatum* latex is less allergenic due to some intrinsic washing that occurs when making the preparation from the bark. If so, commercialization efforts would likely entail a similar process ensuring that low protein levels are maintained so that new allergy problems would be less likely to arise.

Furthermore, in vitro data using LEAP antibodies in rabbits strongly suggest that the lack of cross-reactivity demonstrated here between *H. brasiliensis* and *P. argentatum* is genuine. In these ELISA tests, even highly purified

H. brasiliensis latex was highly cross-reactive with antibodies raised against protein extracts of gloves. No cross-reactivity was observed at all with *P. argentatum* latex.²⁷

Although rubber transferase, an enzyme necessary for the polymerization of isoprene, is common to the rubber particles of all the plants in this paper, *F. elastica* and *P. argentatum* rubber particles contain very few proteins when compared with *H. brasiliensis*. It is thought that many of these additional *H. brasiliensis* proteins are not essential for latex synthesis. A study using mouse polyclonal antibodies to *F. elastica* rubber particles and Western blot analysis indicated relatively few common epitopes in the proteins of *H. brasiliensis* and *P. argentatum* rubber particles (personal communication, Dr. Katrina Cornish).

It is most interesting that these patients did not have any positive skin tests to whole latex from *F. elastica*. This latex is similar to that of *H. brasiliensis* in that rubber particles are found in a milky sap that also contains many different plant proteins. The fact that these subjects were reactive only to *H. brasiliensis* latex demonstrates that the allergen(s) may not be essential for polyisoprene production and may be unique to *H. brasiliensis* latex.

Our seven patients displayed clear immediate hypersensitivity to *H. brasiliensis* latex demonstrated by history and cutaneous tests. They did not demonstrate any skin test reactivity to two other polyisoprene-containing plant sources of rubber. This suggests poten-

tial plant sources of non-allergenic latex in individuals with immediate hypersensitivity to currently available rubber products. It should be noted that all subjects were health care workers and that other patient groups such as children with meningocele may be reactive to non-*H. brasiliensis* latex.

Although both the ammoniated and the nonammoniated *H. brasiliensis* latex gave similar positive results, skin test reactivity was markedly diminished by washing the *H. brasiliensis* rubber particles. This indicates that most of the antigen(s) are not tightly bound to the rubber particle of *H. brasiliensis*. Such washed rubber particles could serve as a safe source of latex for allergic patients and might prevent the sensitization of additional patients.

It should be emphasized that the materials to which subjects did not have positive skin tests could be allergenic. It is possible that patients could become allergic to some other antigen in these substances with repeated exposure.

These results suggest that it may be possible to produce alternative non-cross-reacting rubber products from *H. brasiliensis* or other species including some that grow in the United States.

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Request for reprints should be addressed to:
Andrew B. Carey, MD
510 Lake Blvd., #263
Davis, CA 95616